Paper No. 18

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MICHAEL ROSENBLUM and KAPIL MEHTA

Appeal No. 2005-2133
Application No. 09/226,895[1]

ON BRIEF

Before ELLIS, SCHEINER and GREEN, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 5-9 and 11, the only claims remaining in the application.

Claim 1 is representative:

1. A method of treating an individual having a pathophysiological state selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, lymphomas, and myelomas, comprising the steps of:
a) administering to said individual a pharmacologically effective dose of a retinoid which up-regulates the expression of CD38 antigen; and,
b) administering to the same individual a pharmacologically effective dose of an immunotoxin directed against the up-regulated CD38 antigen.

The references relied on by the examiner are:

Mehta et al. (Mehta '94), "Induction of CD38 by Retinoic Acid in Myeloid Leukemia Cells," Proceedings of the American Association for Cancer Research, Vol. 35, Abstract No. 552 (March 1994)

[1] Application for patent, filed January 7, 1999.

Mehta et al. (Mehta '97), "Retinoic Acid-Induced CD38 Cell Surface Protein as a Target for Immunotoxin Therapy," Proceedings of the American Association for Cancer Research, Vol. 38, Abstract No. 589 (March 1997)

Flavell et al. (Flavell), "Systemic Therapy with 3BIT, a Triple Combination Cocktail of Anti-CD19, -CD22, and -CD38-Saporin Immunotoxins, Is Curative of Human B-Cell Lymphoma in Severe Combined Immunodeficient Mice, Cancer Research, Vol. 57, pp. 4824-4829 (November 1997)

The claims stand rejected as follows:

I. Claims 1, 7-9 and 11 under 35 U.S.C. § 103 as unpatentable over Mehta '97 and Flavell.

II. Claims 1, 5-9 and 11 under 35 U.S.C. § 103 as unpatentable over Mehta '97 and Flavell, further in view of Mehta '94.

We affirm Rejection II and do not reach Rejection I.

DISCUSSION

Initially we note that all of the claims on appeal are rejected over the combined teachings of Mehta '97, Flavell and Mehta '94 (Rejection II), and that Rejection I is incorporated into Rejection II. Therefore, we will address our comments to Rejection II, the more comprehensive of the two rejections. In addition, we note appellants' statement on page 5 of the Brief that "[t]he rejected claims will stand or fall together." Therefore, we shall limit our consideration of the issues raised by this appeal as they pertain to independent claim 1. 37 CFR § 1.192(c)(7) (1999).

Claim 1 is directed to treating acute myeloid leukemia, acute promyelocytic leukemia, lymphoma, or myeloma in an individual, by administering a pharmacologically effective dose of a retinoid which up-regulates the expression of CD38 antigen and a pharmacologically effective dose of an immunotoxin directed against the up-regulated CD38 antigen.

Mehta '97 teaches that "[t]he use of monoclonal antibodies for delivering toxins to cell surface molecules expressed by tumor cells is limited due to heterogeneous expression of the target antigen[,]" but it is possible to circumvent this problem by "inducing high levels of a cell surface target molecules on tumor cells" (Mehta '97, lines 1-4). Mehta '97 demonstrates that the cytotoxicity of IB4/rGel (anti-CD38 monoclonal antibody IB4 conjugated to recombinant plant toxin gelonin) is 4-6 logs more active against CD38-expressing HL-60 leukemia cells than rGel alone, but that pretreatment of the leukemia cells with retinoic acid induces them to express higher levels of CD38, "caus[ing] an additional two-log increase in cell killing by IB4/rGel" (id., lines 11-14). "Normal granulocytes that lacked [ ] basal expression of CD38 could not be induced to express CD38 antigen following [retinoic acid] treatment and were resistant to immunotoxin-induced killing" (id., lines 16-18). Mehta '97 does not describe in vivo administration of retinoic acid and the anti-CD38 immunotoxin – nevertheless, the reference explicitly suggests that "[t]he potent effect of retinoids on cell surface expression of CD38 antigen coupled with the specific cytotoxicity of the IB4/rGel . . . may have clinical utility in terms of treating certain leukemias" (id., lines 18-21).

Mehta '94 is cited as evidence that "the administration of [all-*trans*-retinoic acid] upregulates CD38 target antigen on the surface of myelocytic leukemia cells when administered in vivo" (Answer, page 6), at the dosage required by the claims.

Flavell is cited as evidence that an "anti-CD38 saporin [immunotoxin] is cytotoxic to human lymphoma cells in vivo" (Answer, page 6). Flavell also teaches that "[h]eterogeneity of target antigen expression is a major limiting factor that determines the success of any [antibody]-based therapy for cancer in which delivery of a cytotoxic agent to all malignant cells with growth potential within the tumor is essential for tumor

ablation" (Flavell, page 4824, left-hand column). Flavell attributes this heterogeneity to the possibility that "a small fraction of tumor cells may [be] . . . down-regulated for antigen expression" at any given time "and thereby avoid[ ] killing by [immunotoxin]" (id., page 4829, left-hand column). Flavell concludes that "[o]ne way of overcoming this problem would be to target against two or more molecules on the tumor cell surface in the expectation that multiple antigen-negative tumor cells would occur at a much lower frequency than single antigen-negative cells" (id., page 4824, left-hand column). Using this strategy, Flavell reports that mice injected with a human B-cell lymphoma cell line "are cured when treated with a combination of anti-CD19, -CD22, and CD-38-saporin immunotoxins" (id., abstract), while "[e]ach component [immunotoxin] used individually did not cure the majority of animals but did significantly prolong their survival" (id.).

The examiner bears the initial burden of establishing prima facie obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art." In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). To support a prima facie conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See In re Lowry, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). In addition, the record must provide evidence that those of skill in the art would have had a reasonable expectation of success in doing so. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In this case, we agree with the examiner that the teachings of Mehta '97, Flavell, and Mehta '94 are sufficient to establish that "[i]t would have been prima facie obvious to one of ordinary skill in the art . . . to treat an individual having leukemia or lymphoma

by the administration of retinoic acid followed by and anti-CD38 gelonin conjugate" and that "[o]ne of ordinary skill in the art would have . . . [had] a reasonable expectation of success [because of] the teachings of Flavell [ ] on the efficacious use of the anti-CD38 saponin conjugate in vivo" (paper no. 7, page 2) and "the teaching of Mehta ['94] on the significant increase of CD38 expression observed in vivo following a single oral dose of all-*trans*-retinoic acid" (id., page 3).

Appellants argue that Mehta "suggests retinoid stimulation of CD38 antigen expression may have clinical utility in the treatment of certain leukemias but provides no specific means for accomplishing this" (Brief, page 6). We disagree – indeed, it is hard to imagine how Mehta '97 could be more specific. Mehta '97 demonstrates that pretreatment of leukemia cells with retinoic acid induces them to express elevated levels of CD38, and increases their sensitivity to the anti-CD38 immunotoxin IB4/rGel (without affecting normal cells), and explicitly suggests that this strategy would be effective in vivo as well. Moreover, as discussed above, we agree with the examiner that the prior art would have provided one skilled in the art with a reasonable expectation of success in vivo, as Mehta '94 demonstrates that all-*trans*-retinoic acid up-regulates CD38 in vivo, while Flavell demonstrates that an anti-CD38 immunotoxin is cytotoxic to human lymphoma cells in vivo (Answer, page 6).

Nor are we persuaded by appellants' argument that Flavell "teaches away from the instant invention" (Brief, page 7) by "emphasiz[ing] the simultaneous use of immunotoxins against multiple cellular markers" (id.). According to appellants, "one of ordinary skill in the art, after . . . reading [ ] Flavell, would not resort back to the use of a single immunotoxin, with or without retinoid boosted antigenic expression" (id., page 8).

"A reference may be said to teach away when a person of ordinary skill . . . would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Para-Ordnance Manufacturing Inc. v. SGS Importers International Inc., 73 F.3d 1085, 1090, 37 USPQ2d 1237, 1241 (Fed. Cir. 1995), quoting In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). In this case, both Mehta '97 and Flavell suggest different, but not incompatible, solutions to the problem of heterogeneous expression of tumor antigens in immunotoxin therapy. As discussed above, Mehta '97 suggests that "[a]gents capable of inducing high levels of cell surface target molecules on tumor cells could circumvent this problem[,]" (Mehta '97, lines 3-4) and demonstrates that retinoic acid induces high levels of CD38 on leukemia cells, making the cells much more susceptible to killing by an anti-CD38 immunotoxin than they would otherwise be. The fact that Flavell suggests that "[o]ne way of overcoming [the] problem [of heterogeneity] would be to target against two or more molecules on the tumor surface" (Flavell, page 4824) does nothing to detract from the clinical strategy explicitly suggested by Mehta '97. In other words, we see nothing in Flavell's teachings to discourage one skilled in the art from treating an individual with a retinoid to up-regulate CD38, in order to increase sensitivity to an anti-CD38 immunotoxin. To the extent appellants argue that one would not "resort back to the use of a single immunotoxin," we note that nothing in the open language of claim 1 precludes the administration of more than one immunotoxin.

Finally, we note appellants' argument that "a person having ordinary skill in this art would not be able to determine that [ ] retinoid stimulation of CD38 expression would

enable Flavell's immunotoxin to be used as the sole administered immunotoxin" "without actually attempting the combination" and "without undue experimentation" (Brief, page 8). This argument is not persuasive. First, to the extent that this is an argument that Mehta '97 is not enabling for the claimed in vivo method because it is limited to in vitro administration of retinoic acid and an anti-CD38-gelonin immunotoxin, we note that the examples in present specification are similarly limited to in vitro experimentation. Second, to the extent that this is an argument that Flavell's anti-CD38-saponin immunotoxin would not be expected to exhibit increased cytotoxicity in the same manner as Mehta's anti-CD38-gelonin immunotoxin following up-regulation of CD38 by retinoic acid, we note that appellants have provided no explanation for this assertion, and, in any case, the examiner's proposed combination of the teachings of the references does not require the substitution of immunotoxins.

On this record, we find that the examiner has provided evidence sufficient to establish a prima facie case of obviousness for claim 1, which appellants have not adequately rebutted. As discussed above, claims 5-9 and 11 stand or fall with claim 1. Accordingly, we affirm the examiner's rejections of claims 1, 5-9 and 11 under 35 U.S.C. § 103 (Rejection II) and find it unnecessary to reach Rejection I.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Joan Ellis
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Lora M. Green
Administrative Patent Judge

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